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4 October 2001

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(54) Title: **ENHANCING DRUG DELIVERY ACROSS AND INTO EPITHELIAL TISSUES USING OLIGO ARGININE MOIETIES**

(57) Abstract: This invention provides compositions and methods for enhancing delivery of drugs and other agents across epithelial tissues, including the skin, gastrointestinal tract, pulmonary epithelium, and the like. The compositions and methods are also useful for delivery across endothelial tissues, including the blood brain barrier. The compositions and methods employ a delivery enhancing transport that has sufficient guanidino or amidino sidechain moieties to enhance delivery of a compound conjugated to the reagent across one or more layers of the tissue, compared to the non-conjugated compound. The delivery enhancing polymers include, for example, poly-arginine molecules that are preferably between about 6 and 25 residues in length.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE, MEDLINE, CANCERLIT, BIOSIS, DISSERTATION ABS PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2 094 658 A (ALLELIX BIOPHARMA) 24 October 1993 (1993-10-24) page 1, line 5 - line 9 page 2 -page 3, line 13 examples 2,3 claims	3,38
X	WO 98 52614 A (ROTHBARD JONATHAN B ;UNIV LELAND STANFORD JUNIOR (US); WENDER PAUL) 26 November 1998 (1998-11-26) page 3, line 29 -page 4, line 6 page 6, line 8 - line 27 examples 4,7,9,11A,12 figures 2B,2C,2E2F,5A-5C sequence 19	3,38



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

20 November 2000

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>ZIPING WEI ET AL: "SYNTHESIS OF OLIGOARGININE-OLIGONUCLEOTIDE CONJUGATES AND OLIGOARGININE-BRIDGED OLIGONUCLEOTIDE PAIRS"</p> <p>BIOCONJUGATE CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, vol. 5, no. 5, 1 September 1994 (1994-09-01), pages 468-474, XP000465958</p> <p>ISSN: 1043-1802</p> <p>abstract</p> <p>page 469; table 1</p> <p>page 470; figure 1</p>	3
Y	<p>WO 92 07871 A (ALLELIX BIOPHARMA)</p> <p>14 May 1992 (1992-05-14)</p> <p>examples</p>	3,38
X	<p>CHEMICAL ABSTRACTS, vol. 123, no. 7, 1995</p> <p>Columbus, Ohio, US;</p> <p>abstract no. 79357,</p> <p>SUMNER-SMITH, M. ET AL: "Antiherpetic activities of N-.alpha.-acetyl-nona-D-arginine amide acetate"</p> <p>XP002086015</p> <p>abstract</p> <p>& DRUGS EXP. CLIN. RES., 1995, VOL. 21, NO. 1, PAGE(S) 1-6,</p>	3,38
Y	<p>EP 0 599 303 A (TAKEDA CHEMICAL INDUSTRIES LTD) 1 June 1994 (1994-06-01)</p> <p>examples</p> <p>figures</p>	3,38
Y	<p>BUSCHLE M. ET AL: "Transloading of tumor antigen-derived peptides into antigen-presenting cells"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 1997, VOL. 94, NO. 7, PAGE(S) 3256-3261,</p> <p>XP002086009</p> <p>page 3256</p> <p>page 3259</p> <p>figures</p>	3,38
Y	<p>UCHIDA D. ET AL: "Polycations decrease the transepithelial resistance of cultured tracheal epithelial cells"</p> <p>CHEST, 1992, VOL. 101, NO. 3 (SUPPL.), PAGE(S) 33S,</p> <p>XP002086010</p> <p>the whole document</p>	3,38

INTERNATIONAL SEARCH REPORT

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NATSUME, H. ET AL: "Screening of absorption enhancers for nasal peptide and protein delivery" 23RD. PROC. INT. SYMP. CONTROLLED RELEASE BIOACT. MATER., JULY 7-10, 1996 PAGES 481-482, XP002086011 see paragraph INTRODUCTION figure 1C ---	3,38
Y	ELFERINK JG: "Changes of plasma membrane permeability in neutrophils treated with polycations." INFLAMMATION, APR 1991, VOL. 15, NO. 2, PAGE(S) 103-15, XP002086012 paragraph [RESULTS] ---	3,38
Y	MAUERSBERGER B ET AL: "Studies on the cytotoxicity of poly-L-arginine, poly-L-lysine and DEAE-dextran in L-cells and mouse embryonic fibroblasts." EXP PATHOL (JENA), 1977, VOL. 13, NO. 4-5, PAGE(S) 268-73, XP002086013 abstract paragraph [RESULTS] ---	3,38
Y	BURTON, K. A. ET AL: "Basic polyelectrolytes and protein transport across the newborn pig intestine" J. PHYSIOL., 1970, VOL. 211, NO. 2, PAGE(S) 27P-28P, XP002086014 the whole document ---	3,38
X	US 5 804 604 A (PABO CARL ET AL) 8 September 1998 (1998-09-08) example 4 ---	3,38
P,Y	BABIUK S ET AL: "Cutaneous vaccination: the skin as an immunologically active tissue and the challenge of antigen delivery" JOURNAL OF CONTROLLED RELEASE, NL, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, vol. 66, no. 2-3, May 2000 (2000-05), pages 199-214, XP004193068 ISSN: 0168-3659 page 205, right-hand column, last paragraph ---	3,38
Y	GB 744 988 A (ALLEN & HANBURYS LTD. ET AL.) 15 February 1956 (1956-02-15) examples 8,19 ---	3,38

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 09, 31 July 1998 (1998-07-31) & JP 10 095738 A (T T S GIJUTSU KENKYUSHO:KK), 14 April 1998 (1998-04-14) abstract	3,38
Y	--- TAKAO AOYAGI ET AL: "POLYMERIZATION OF BENZALKONIUM CHLORIDE-TYPE MONOMER AND APPLICATION TO PERCUTANEOUS DRUG ABSORPTION ENHANCER" JOURNAL OF CONTROLLED RELEASE,NL,ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, vol. 13, no. 1, 1 July 1990 (1990-07-01), pages 63-71, XP000142028 ISSN: 0168-3659 page 67, right-hand column -page 69, right-hand column, line 3 figures 3-5	3,38
Y	--- HOSOYA O ET AL: "EFFECT OF SERERAL HYDROPHILIC POLYMERS ON THE PERMEATION OF MORPHINE AND SALICYLIC ACID THROUGH EXCISED HARELESS RAT SKIN" CHEMICAL AND PHARMACEUTICAL BULLETIN,JP,PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, vol. 46, no. 5, 1 May 1998 (1998-05-01), pages 882-885, XP000755081 ISSN: 0009-2363 abstract page 883, right-hand column -page 885 figure 2	3,38
X	--- HULSMANN ANTHON R ET AL: "Permeability of human isolated airways increases after hydrogen peroxide and poly-L-arginine." AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, vol. 153, no. 2, 1996, pages 841-846, XP000953296 ISSN: 1073-449X abstract page 843, left-hand column, last paragraph; figure 3 page 844, left-hand column, last paragraph page 845, left-hand column, last paragraph -page 846 --- -/--	3,38

INTERNATIONAL SEARCH REPORT

Int'l Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>TZAN CHYANSONG J ET AL: "Modification of epithelial permeability by cationic polypeptides." AMERICAN JOURNAL OF PHYSIOLOGY, vol. 265, no. 6 PART 1, 1993, pages C1637-C1647, XP000953297 ISSN: 0002-9513 abstract figure 1 page C1683, right-hand column, paragraph RESULTS -page C1639, right-hand column, line 28 figures 4,8,9 page 1646, right-hand column</p>	3,38
Y	<p>COYLE ANTHONY J ET AL: "Role of cationic proteins in the airway: Hyperresponsiveness due to airway inflammation." AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, vol. 150, no. 5 PART 2, 1994, pages S63-S71, XP000953278 ISSN: 1073-449X abstract page 565, left-hand column; figure 3 page 568; figure 8 page 569, left-hand column, line 12 - line 31 figure 10</p>	3,38
Y	<p>PETERSON P K ET AL: "POLY AMINO-ACID ENHANCEMENT OF BACTERIAL PHAGOCYTOSIS BY HUMAN POLYMORPHONUCLEAR LEUKOCYTES AND PERITONEAL MACROPHAGES" INFECTION AND IMMUNITY, vol. 43, no. 2, 1984, pages 561-566, XP002153308 ISSN: 0019-9567 abstract page 563, left-hand column; figure 1 page 563, left-hand column, last paragraph -page 564, left-hand column, line 14</p>	3,38
Y	<p>GAMA LUCIO ET AL: "Ca²⁺-sensing receptors in intestinal epithelium." AMERICAN JOURNAL OF PHYSIOLOGY, vol. 273, no. 4 PART 1, October 1997 (1997-10), pages C1168-C1175, XP000953281 ISSN: 0002-9513 abstract figures 3-6</p>	3,38

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PCT/US 00/23440

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	COLIN M ET AL: "Liposomes enhance delivery and expression of an RGD-oligolysine gene transfer vector in human tracheal cells." GENE THERAPY, vol. 5, no. 11, November 1998 (1998-11), pages 1488-1498, XP000953285 ISSN: 0969-7128 abstract figures	3,38
Y	--- UCHIDA DEREK A ET AL: "Cationic proteins increase the permeability of cultured rabbit tracheal epithelial cells: Modification by heparin and extracellular calcium." EXPERIMENTAL LUNG RESEARCH, vol. 22, no. 1, 1996, pages 85-99, XP000953298 ISSN: 0190-2148 abstract	3,38
Y	--- PERR H A ET AL: "PROTAMINE SELECTIVELY INHIBITS COLLAGEN SYNTHESIS BY HUMAN INTESTINAL SMOOTH MUSCLE CELLS AND OTHER MESENCHYMAL CELLS" JOURNAL OF CELLULAR PHYSIOLOGY, vol. 140, no. 3, 1989, pages 463-470, XP000953287 ISSN: 0021-9541 abstract	3,38
Y	--- TZAN CHYANSONG J ET AL: "Mammalian urinary bladder permeability is altered by cationic proteins: Modulation by divalent cations." AMERICAN JOURNAL OF PHYSIOLOGY, vol. 267, no. 4 PART 1, 1994, pages C1013-C1026, XP000953279 ISSN: 0002-9513 abstract	3,38
Y	--- SANTANA A ET AL: "Inflammatory responses induced by poly-L-arginine in rat lungs in vivo." AGENTS AND ACTIONS, vol. 39, no. 3-4, 1993, pages 104-110, XP000953282 ISSN: 0065-4299 abstract -----	3,38

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim(s) 3 and 38 are directed to a diagnostic method practised on the human or animal body, a search has been carried out, based on the alleged effects of the conjugate.
2. ☒ Claims Nos.: **1, 2, 4-37, 39-80, 99-101 and part of 3 and 38**
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
3 in part, and 38

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 3 in part, and 38

Method for enhancing transport of a compound across tissue, in which the compound is a contrast agent.

2. Claims: 3, 44, 48 in part, and 51-53

Method for enhancing transport of a compound across tissue, in which the compound is an antifungal agent.

3. Claims: 3, 44, 48 and 56 in part

Method for enhancing transport of a compound across tissue, in which the compound is an antiproliferative agent.

4. Claims: 3, 44 and 56 in part, and 81-84, 102, 106 and 107

Method for enhancing transport of a compound across tissue, in which the compound is an immunosuppressive agent.

5. Claims: 3, 48, 56 and 102 in part, and 49, 50, and 104

Method for enhancing transport of a compound across tissue, in which the compound is an antiinflammatory corticosteroid.

6. Claim : 3 in part

Method for enhancing transport of a compound across tissue, in which the transport enhancing polymer is a non-natural peptide other than oligo arginine.

7. Claim : 40

Method for enhancing transport of a compound across tissue, in which the transport enhancing polymer is a non-peptide derived from oligo arginine.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 2, 4-37, 39-80, 99-101 and part of 3 and 38

In view of the

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 00/23440

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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